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DISTAMYCIN ANALOGS AS POTENTIAL ANTIMALARIALS.(U)
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Distamycin Analogs as Potential Antimalarials

Final Scientific Report

Henry Rapoport

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Antimalarials; Distamycin; Permethyldistamycin; Acylamidines; Acylguanidines

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New synthetic procedures have been developed which resulted in efficient syntheses of the permethyl analogues of distamycin, an antiviral antibiotic. Methods were also developed for selective acylations among amine, amidine, and guanidine functionalities. None of the compounds synthesized were effective against malaria.

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I. Narrative Summary

A synthesis has been developed of an analogue of distamycin A, a pyrrolic oligopeptide possessing antiviral and antibiotic activity, in which each of the three pyrrole rings is fully methylated. This structural modification results in pyrrole rings which are extraordinarily electron rich and required the development of a new synthetic approach to these polypyrrolic amides. The key reactions involved development of a general method for the synthesis of 3-aminopyrroles and for formation of an amide bond between a pyrrole-2-carboxylic acid and these 3-aminopyrroles. Since the acid is hindered, a poor electrophile, and acid sensitive, while the amine is unstable and a hindered, weak nucleophile, amide bond formation under the usual conditions was poor. A very efficient method, however, was developed involving the isolation of 1-hydroxybenzotriazole active ester prepared in situ from another active ester. Neither the mono-, di-, nor tripyrrolic permethyl analogues were effective antimalarials.

Since these compounds, and their relatives, contain both amino and amidino, or guanidino, functions, it was necessary to develop methods for unambiguous assignment of the site of acylation. This was done through a study of the ultraviolet absorption spectra of the acylated products. If the amidine or guanidine has been acylated, the product possesses a chromophore that is pH dependent, whereas if an amide was formed, the chromophore is independent of pH.

II. Bibliography

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